

REMARKS/ARGUMENTS

Claims 1, 4, 7, 10-14, 17-22 and 24-29 are active.

Claim 1 is amended to define the concentration ranges of (A) and (B) as described on page 8, lines 2-3 and page 11.

New Claims 28 and 29 find support from the end point 2% in Table 4 coupled with the range presented on page 11. See also, *In re Lukach*, 442 F.2d 967, 970 (CCPA 1971), *In re Wertheim*, 541 F.2d 257 (CCPA 1976), the claims defined a range of 35-50% and were held to be supported by the underlying disclosure having examples at 35% and 50%, and *Kolmes v. World Fibers Corp.*, 107 F.3d 1534 (Fed. Cir. 1997), the claims defined a range of 8-12 turns where the underlying disclosure described 4-12 turns, and stated that 8 turns was optimal, and the application at issue claimed 8-12 turns.

No new matter is added.

Applicants thank Examiners Haghigatian and Chui for the courtesy of discussing this case with their undersigned representative. During this discussion, the data presented in the specification was discussed in relation to the claims and the art of record. As noted in the Interview Summary record of this case, the Examiner's found that only the result in Table 4 were relevant to the claims and that the Tsuk patent teaches the utility of menthol as a skin penetration enhancer.

The present claims have been amended to more particularly define the concentration ranges of (A) and (B) consistent with the data presented in Table 4 and the attached Rule 132 Declaration, particularly showing that within the concentration of (B) recited in the claims, the skin permeability of the statin (A) was higher, something that Applicants believe would not have been reasonably predictable based on the teachings of the cited references.

The obviousness rejection of Claims 1, 4, 7-14, 17-22, and 24-27 based on Sawayanagi, Hidaka, and Dasseux is traversed.

Sawayanagi is drawn to “[a] plaster comprising pranoprofen, a hydrophilic or hydrophobic base component, and an enhancer” (emphasis added, see the Abstract of Sawayanagi). Sawayanagi, at column 2, lines 28-31, describes preferred enhancers as being “propylene glycol, diisopropyl adipate, 1-menthol, and benzyl alcohol.” Hidaka describes “[a] plaster comprising the film layer which is composed of a film having 0.5 to 4.8 μm thickness....and an adhesive layer (a) which contains a transdermally absorbable drug and is laminated on one surface of said film layer in 2 to 60 μm thickness [that] enables transdermal absorption of a clinically effective amount of a drug with skin rashes reduced” (see the Abstract of Hidaka). The Examiner relies again on Dasseux to partially remedy the deficiencies of Sawayanagi and Hidaka by providing “croscarmellose sodium” (see page 7 of the Official Action),

Further in the section responding to Applicants previous arguments, the Examiner cites to US 4,933,184 to Tsuk in support of the rejection that menthol has utility to enhance percutaneous absorption of systemically active drugs (see page 8 of the Action) thereby maintaining a reasonable expectation of success.

While Applicants do not dispute that what is attributed to those newly cited references on pages 8-9 of the Action teach such a utility of menthol for some of the drugs that are listed, this still does not provide a reasonable expectation of success, particularly as the present claims defined two specific compounds (or salts thereof) and these compounds are structurally quite different as Applicants have explained and illustrated in prior responses.

Pitavastatin and atorvastatin in addition to having different biological functions compared to the references relied upon to support the contention that menthol increases percutaneous absorption, have different mechanisms of action, have very different structures,

and different physical properties. Thus, while 1-menthol, employed by Sawayanagi or Tsuk or any of the other references relied upon in the rejection is taught as an enhancer that may promote percutaneous absorption of pranoprofen or other structurally unrelated actives (compared to what is claimed), there is no reasonable expectation to think that it would promote percutaneous absorption of a different chemotype (e.g., a statin) that has different biological properties, a different mechanism of action, a different chemical structure, and different physical properties from pranoprofen and the other actives “suggested” in the cited art. See also, *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 87 U.S.P.Q.2D 1452 (Fed. Cir. 2008): “To the extent an art is unpredictable, as the chemical arts often are, KSR’s focus on these “identified, predictable solutions” may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.”

Presuming that a *prima facie* case of obviousness has been made, Applicants presentation of improved results, in the specification and by way of the attached Declaration, is a sufficient secondary consideration to rebut such a *prima facie* case of obviousness. “Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness.” No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)”

The terpene at certain concentrations improves the percutaneous absorption of pitavastatin, atorvastatin, a salt of pitavastatin, or a salt of atorvastatin. For example in Table 4, presented on page 26 shows the improved permeability performance of both pitavastatin and atorvastatin in the presence of 2% 1-menthol. Further, the data shown in the attached Declaration, when considered in view of the comparative data presented in Table 4 of the

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specification, shows that at concentrations 0.1 to 10 % by mass, e.g., 2 to 10% by mass of (B) (see Claim 28) increased the permeability coefficient, an effect that would not have been reasonably predictable for the pitavastatin, atorvastatin, or salts thereof based on the accumulated teachings of Sawayanagi, Hidaka, and Dasseux even with the other references cited in the rejection itself as the ability of a substance to improve percutaneous absorption of a target drug greatly varies depending on the type of substance and the drug, and there is no way to reasonably predict, *a priori*, what effect a particular substance will have on a particular target drug.

Reconsideration and withdrawal of the rejection is requested.

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A Notice of Allowance is also requested.

Respectfully submitted,

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